



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

The Reply



Dr. Quinn makes the important point that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and Coronavirus disease 2019 (COVID-19) crisis creates a context to consider when proposing treatment and undertaking clinical trials.¹ The setting is a new medical problem that is serious and resulting in record numbers of hospitalizations and deaths. That is very different from chronic disease where there is already a base of treatment and the next clinical trial can test a single drug on top of guidelines-directed therapy and take many years to complete. Such trials in cardiovascular medicine may enroll thousands of patients. The COVID-19 crisis is a global catastrophe that initially called for an immediate medical response in hospitals around the world. When it became clear within a few months that hospitalization could not save all the patients, there was a very strong medical, ethical, and moral mandate for empiric early, ambulatory, compassionate treatment with the aim of reducing the intensity and duration of symptoms, and via that mechanism, reduce the risks of hospitalization and death.² Like all serious viral infections, SARS-CoV-2 appears to be incurable with short courses of single drugs. The innovation occurred when multiple drugs and nutraceuticals were used in combination.^{3,4} The infection was not cured; however, the severity and duration of symptoms was sufficiently reduced to alter the patient's course and avoid hospitalization and death by ~85%.⁵ Randomized trials of using 4-6 drugs in combination vs matching placebos in thousands of outpatients are not forthcoming. Thus, we are aligned with Dr. Quinn, that an adaptive approach with continual review of the literature

for signals of benefit and acceptable safety with either novel or existing drugs is the appropriate path forward, building upon algorithmic regimens we have devised or similar ones as they appear in the medical literature.⁶

Peter A. McCullough, MD, MPH
Department of Internal Medicine,
Division of Cardiology, Texas A &
M University College of Medicine,
Dallas

<https://doi.org/10.1016/j.amjmed.2021.02.023>

References

1. McCullough PA, Oskoui R. Early multidrug regimens in new potentially fatal medical problems. *Rev Cardiovasc Med* 2020;21(4):507–8.
2. McCullough PA, Kelly RJ, Ruocco G, et al. Pathophysiological basis and rationale for early outpatient treatment of SARS-CoV-2 (COVID-19) infection. *Am J Med* 2021;134(1):16–22.
3. Derwand R, Scholz M, Zelenko V. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study. *Int J Antimicrob Agents*. 2020;56(6):106214.
4. Procter BC, Ross C, Pickard V, Smith E, Hanson C, McCullough PA. Clinical outcomes after early ambulatory multidrug therapy for high-risk SARS-CoV-2 (COVID-19) infection. *Rev Cardiovasc Med* 2020;21(4):611–4.
5. Procter BC, Ross C, Pickard V, Smith E, Hanson C, McCullough PA. Early ambulatory multidrug therapy reduces hospitalization and death in high-risk patients with SARS-CoV-2 (COVID-19). *Authorea* January 07, 2021. <https://doi.org/10.22541/au.161000355.54720791/v1>.
6. McCullough PA, Alexander PE, Armstrong R, et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). *Rev Cardiovasc Med* 2020;21(4):517–30.

Funding: None related.

Conflicts of Interest: Nothing to disclose.

Authorship: The author had access to the data and wrote the manuscript.

Requests for reprints should be addressed to Peter A. McCullough, MD, MPH, Department of Internal Medicine, Division of Cardiology, Texas A & M College of Medicine, 3409 Worth Street, Suite 500, Dallas, TX 75246.

E-mail address: peteramccullough@gmail.com